states of excitement, agitation, or emotional tension. All patients were classified, therefore, according to their psychomotor state. In the overactive group were classed excited, aggressive, or emotionally unstable schizophrenics, manics, agitated depressives and seniles, and anxious neurotics, while the inhibited group contained catatonic stupors and detached schizophrenics, retarded depressives, and apathetic neurotics. Detached schizophrenics who became periodically impulsive were placed in a separate category.

The results shown in Table III are somewhat surprising. Although more patients recovered in the overactive group and more inhibited patients did not improve, if the recovered

TABLE III.—*Results Analysed According to Psychomotor State*

| Psychomotor State | Recovered | | Much Improved | | Moderately Improved | | Slightly Improved | | Not Improved | | Total No. of Cases |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % | No. | % | |
| Overactive .. | 8 | 6 | 17 | 13 | 31 | 25 | 35 | 28 | 35 | 28 | 126 |
| Inhibited .. | 1 | 2 | 9 | 17 | 15 | 29 | 6 | 12 | 21 | 40 | 52 |
| Inhibited with impulsive outbursts | — | — | 1 | 6 | 7 | 39 | 8 | 44 | 2 | 11 | 18 |
| Total .. | 9 | 5 | 27 | 14 | 53 | 27 | 49 | 25 | 58 | 29 | 196 |

and much improved are grouped together on the one hand and the slightly improved and not improved on the other, the results are almost identical in both inhibited and overactive patients. This suggests that some revision is needed in the conception of chlorpromazine as being mainly a symptomatic treatment for excited states.

### Chlorpromazine and Leucotomy

The effects of chlorpromazine have often been compared to those of leucotomy. It might therefore be supposed that patients in whom leucotomy had failed would equally fail to respond to chlorpromazine, and, conversely, that chlorpromazine might prove a useful prognostic indicator for leucotomy. Neither of these suppositions is borne out by the results in this series.

The results in 28 patients in the series who had previously been leucotomized were as follows: much improved, 3 (11%); moderately improved, 6 (21%); slightly improved, 11 (39%); not improved, 8 (29%). These results do not vary significantly from those in the series as a whole, and lend further support to the view that chlorpromazine can be of value in prognostically poor cases.

On the other hand, four patients who failed to respond in any way to chlorpromazine have made a very good immediate response to leucotomy, though it remains to be seen whether this will be maintained.

### Side-Effects and Toxic Reactions

The various side-effects and toxic reactions recorded in the literature were noted in this series, but, as their occurrence in a much larger number of cases is the subject of a separate communication, no details are mentioned here.

### Summary and Conclusions

The results in 205 patients treated with chlorpromazine are examined.

A tentative scheme of dosage and duration of treatment is discussed. It is not felt that the intramuscular route offers any advantages over the oral.

Results in the different diagnostic categories suggest that chlorpromazine may play a useful part in the treatment of acute states of excitement of all sorts, in neurotics in whom tension or anxiety is a prominent symptom, and in some depressive patients in whom E.C.T. has proved ineffective.

The most striking results, however, were obtained in chronic psychotic patients in whom the prognosis would normally be very bad. It enabled a few of these patients to be discharged and many more to make a good hospital adjustment.

In chronic patients it was felt that the chief part played by chlorpromazine was to make possible the rehabilitation of those in whom this was formerly impossible and that, while in some relapse occurred immediately treatment was stopped, in others improvement still continued.

There seemed to be little difference between its effect on overactive and inhibited patients.

As good results were found after leucotomy as in other chronic patients.

I wish to thank Messrs. May & Baker for kindly making supplies of chlorpromazine available for this trial; Dr. Robert Forgan, of May & Baker, for his very valuable help and advice; and Dr. H. C. Beccle, medical superintendent of Springfield Hospital, for much helpful criticism in the preparation of this paper.

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# CHLORPROMAZINE IN TREATMENT OF ELDERLY PSYCHOTIC WOMEN

BY

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One of the difficult nursing problems in a mental hospital concerns the group of elderly long-stay patients who suffer from periods of restlessness, confusion, and disorientation or who are continually in a state of agitation, with stereotyped speech and activity. The Board of Control (1954) stated that, "on January 1, 1953, 28.8% of the mental hospital population were over the age of 65 and two-thirds of these were women."

A related problem is the shortage of nursing staff, owing to which large wards of noisy, difficult patients have to be in the care of too few nurses, or patients have to be left at night with inadequate supervision. It is hoped to show that chlorpromazine ("largactil") may play a part in the solution of these problems.

Since interest in the psychiatric use of chlorpromazine was roused by Sigwald and Bouttier (1953), who summarize the literature, and by Ey and Bérard (1952), who used it as a method of prolonged sleep treatment (*cure de sommeil*) in psychiatric patients, various authors in this country have published series of cases suggesting its value when tension and agitation predominate—Anton-Stephens (1954) on psychiatric patients with varying diagnoses, Garmany *et al.* (1954) in psychoneurosis, Elkes and Elkes (1954) in psychosis, and Howell *et al.* (1954) in geriatrics.

The present series is a group of elderly psychotic women with varying diagnoses but having in common

the fact that they became nursing problems because they were noisy, abusive, violent, and destructive, or required constant attention for feeding and dressing.

### Case Material

Forty-eight women aged from 58 to 87 were chosen, all being nursing problems to a varying degree. Many had been in hospital for several years, but some had been recently admitted with diagnoses of senile dementia. Table I shows the age grouping and the diagnoses.

TABLE I.—*Age Grouping and Diagnoses*

| Age | No. | Diagnoses | No. |
|---|---|---|---|
| 58 .. | 1 | Schizophrenia (including paranoia paraphrenia) | 13 |
| 60–70 .. | 18 | Agitated depression .. .. .. .. | 6 |
| 71–80 .. | 22 | Dementia (all organic causes) .. .. .. | 29 |
| Over 80 .. | 7 | | |
| Total .. | 48 | Total .. | 48 |

Two of the patients were later withdrawn from the trial —one because she developed jaundice, and the other because she fell and sustained a fractured femur.

### Method

These 48 patients were divided into two groups : the parenteral Group P (22 patients), beginning treatment by injection, and the oral Group O (26 patients), receiving oral treatment only.

*Group P.*—Eleven of these patients were given a course of 50 mg. of chlorpromazine thrice daily by injection for one week, followed by 50 mg. thrice daily by mouth for three weeks. At the same time the other 11 patients received one week's treatment with an equivalent volume of inert control injection followed by three weeks' treatment with inert tablets. At the time of the experiment no one knew into which half of the group each patient fell. At the end of the first four weeks the two half groups were reversed, so that those receiving chlorpromazine now received control tablets while those on control tablets received chlorpromazine. For reasons discussed later, it was felt that patients should not receive further parenteral therapy, and oral therapy alone was used in the second month.

*Group O.*—This group originally consisted of 26 patients, half of whom began treatment with chlorpromazine, 25 mg. thrice daily for three days, then 50 mg. thrice daily for ten days, and 75 mg. thrice daily for two weeks. It was from this half of the group that the two cases had to be withdrawn. The other half received corresponding numbers of control tablets, and after a month the two halves of the group were reversed in a manner similar to that described above.

### Summary of Results

Table II shows the number of patients in each group falling into categories of improvement. Three degrees of improvement were considered :

\+ Some improvement: somewhat less agitated and restless; able to sleep without sedative.

\++ Definite improvement: more rational and talkative; less restless; not so disturbed by delusions.

\+++ Marked improvement: able to look after herself, whereas she had been unable to do so hitherto; spontaneous conversation; could take part in social activities.

Dealing first with Group P, and taking the two treatment subgroups together and the two control subgroups together —that is, A1 and B2, also A2 and B1 (see Table II)—and grouping the results as either improved or not improved, we get $\chi^2 = 17.8$ and $P \leq 0.001$. The difference between the treatment and the control groups was highly significant. Similarly, in Group O $\chi^2 = 16.3$ and $P \leq 0.001$—again highly significant.

TABLE II.—*Number of Patients Falling into Various Categories of Improvement*

| | Group P | | | | Group O | | | |
|---|---|---|---|---|---|---|---|---|
| | Improvement | | | No Change or Relapse | Improvement | | | No Change or Relapse |
| | + | ++ | +++ | | + | ++ | +++ | |
| 1st month: | | | | | | | | |
| Treatment (A1) .. | 4 | 5 | 2 | 0 | 2 | 2 | 3 | 4 |
| Control (B1) .. | 1 | 0 | 0 | 10 | 3 | 2 | 0 | 8 |
| 2nd month: | | | | | | | | |
| Now control (A2) .. | 3 | 0 | 0 | 8 | 2 | 1 | 0 | 8 |
| Now treatment (B2) | 2 | 3 | 2 | 4 | 2 | 8 | 2 | 1 |

The two patients who were withdrawn were in subgroup A1 of Group O.

It is necessary to differentiate clinically between those patients who improved on treatment and relapsed when receiving control tablets and those who improved when receiving control tablets or in whom no change took place. Combining Groups O and P, patients were found to fall into six further groups (Table III). It will be seen that 28 (60.9%) cases showed some degree of improvement with chlorpromazine, while if group 3 is added the figure is 33 (71.7%).

TABLE III.—*Number of Patients in Each Category of Improvement*

| Group | | No. of Patients |
|---|---|---|
| 1 | Improved on treatment. Relapsed on control .. .. | 12 |
| 2 | No change on control. Improved on treatment .. .. | 16 |
| 3 | Improved on treatment. Maintained on control .. .. | 5 |
| 4 | Improved on control. Maintained on treatment .. .. | 4 |
| 5 | Improved on treatment. Improved more on control .. | 1 |
| 6 | No change on control or on treatment .. .. .. | 8 |
| | Total .. | 46 |

*Note:* Group 3 probably corresponds to group 1, but where the effect of treatment was prolonged into the control period.

When assessed according to diagnosis, there was no significant difference between the groups.

### Comment on the Series

It was very noticeable that patients on treatment looked ill, with pinched, drawn faces, and pallor, though there was no subjective complaint.

Cases of pyrexia and tachycardia were much more frequent in the group receiving parenteral therapy. When an inflammatory area developed at the injection site, this was associated with pyrexia (four cases), but five more cases had temperatures of 100–103° F. (37.8–39.4° C.) (axillary), usually lasting four or five days and subsiding without other medication and without discontinuing the drug. Only two of the Group O cases had temperatures during the period of treatment.

TABLE IV.—*Liver-function Tests on Patient who Became Jaundiced*

| Date | Van den Bergh Direct | Serum Bilirubin mg./100 ml. | Ser. Alk. Phosphat. Units | Thym. Turb. Units | Blood Urea mg./100 ml. | Protein (g.%) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Total | Alb. | Glob. | A/G Ratio |
| 8/9 | + | 4·6 | 55·1 | 3·0 | 30 | 6·66 | 3·77 | 2·89 | 1·3 : 1 |
| 15/9 | | 1·8 | | | | | | | |
| 24/9 | | 1·5 | | | | | | | |
| 27/9 | — | 0·97 | 45·7 | 4·0 | 32 | 6·86 | 3·46 | 3·40 | 1·02 : 1 |
| 11/10 | — | 1·2 | 30·4 | 0·7 | 36 | 7·9 | 5·3 | 2·6 | 2·04 : 1 |

One case of jaundice has so far occurred. This first appeared 21 days after the beginning of treatment, and was preceded by two days' pyrexia to 102° F. (38.9° C.). The patient had received a total of 2,700 mg. of chlorpromazine at that time. It was noticed that her skin appeared yellow before the conjunctivae. A bradycardia down to 40 a minute developed, and persisted for three weeks. Urine was dark, but stools were not noticeably pale. Liver-function tests on this patient are shown in Table IV.

The following report is that of another patient who received chlorpromazine, developed jaundice, and then

recovered. Some weeks later she died of bronchopneumonia, an illness believed to have been quite unconnected with the jaundice.

A married woman aged 79 was admitted to a geriatric ward, where a diagnosis of senile dementia was made and she was given chlorpromazine both orally and parenterally. After 32 days, and after receiving a total dosage of 3,875 mg. in two courses separated by ten days, she developed jaundice. This occurred on the fourth day of the second course, when only 750 mg. of chlorpromazine had been given; treatment was discontinued. The jaundice subsided in two weeks. She was admitted to this hospital two months later, dying two weeks after admission. The cause of death, bronchopneumonia and pulmonary embolus, was confirmed at necropsy. Section of the liver showed nothing specific except moderate fatty changes and patchy lymphocytic infiltration in the portal areas.

Drowsiness, sometimes accompanied by a subjective giddiness, occurred in 11 cases. It usually passed off after the first two weeks, and in itself was not a serious complication. It was probably responsible, however, for the case of fractured neck of the femur. In elderly patients, in whom the risk of fracture is already present, the unsteadiness or drowsiness may well lead to a fall. This patient fell about one and a half hours after receiving her tablets. All patients were put to bed—though not all could be kept there—for an hour after receiving treatment, and this one fell soon after getting up.

Senile patients often become noisy, confused, and deluded after fractures, and chlorpromazine has been found very useful in such cases. It is noteworthy that, in the two cases in which fractures have occurred in elderly patients who were on chlorpromazine at the time, the common agitated, confused state did not develop. One of these has just been described, and the second case occurred while electroplexy was being given as well as chlorpromazine.

Other mild side-effects were dryness of the mouth, abdominal pain and diarrhoea, polyuria, and rashes. These responded to simple medication and did not warrant discontinuation of treatment.

## Discussion

These results show that chlorpromazine has been effective in improving the general behaviour of a group of elderly psychotic women, though this improvement was not uniformly good. Most of them became more manageable, with few noisy outbursts or demonstrations of violence, and were able to feed and dress themselves. While several cases showed striking improvement, no patient in this group was considered fit for discharge, although two were going out with relatives for week-ends. Several patients have become employable, and have been able to take part in the social activities of the ward, the cinema, and coach rides.

It is necessary to compare these results with those which could be obtained using other forms of treatment at present available. Firstly, of course, these patients were chosen from those who had not responded adequately to other forms of sedation—all had been receiving large and frequent doses of paraldehyde or barbiturates, while several had had maintenance electroplexy. When they were included in the series and had this sedation stopped, many of them became very noisy and difficult; these patients were subsequently found to be having control tablets. Sedation by paraldehyde, barbiturates, or bromides suffers from the disadvantage that large doses are needed for long periods, and, even if the drugs are varied, problems of tolerance, habituation, drug rashes, and bromism arise. The patients are drowsy and confused, and unable to look after themselves, whereas after the first two weeks on chlorpromazine drowsiness usually passes off and the sedative effect seems to continue. After the drug has been discontinued the effect persists for a period varying from two to six weeks, and thus it may be possible to give periodic courses instead of continuous treatment. There seems to be no indication for routine parenteral therapy, even for a short introductory period, unless there is an urgent need to quiet a confused or agitated patient.

Adequate dosage is usually 150–200 mg. in divided doses daily, and the last dose should be given fairly late in the evening so as to ensure a good night's sleep.

I would like to stress the value of chlorpromazine in the treatment of restlessness following fractures in elderly patients. This is rapidly controlled, so that adequate operative and splinting technique may be carried out. It is in this type of case that the intramuscular route should be used, at least for the first few days. It is important to realize that in elderly patients, with the risk of fracture, use of the drug may be an additional hazard: it is little consolation to know that it is effective in the treatment of the condition it has helped to cause. Thus patients must be encouraged to rest for some considerable time after they have received their tablet—one to two hours if possible—and the dosage should be regulated so that the minimum is given to produce a therapeutic effect.

The question of the occurrence of jaundice is one of great importance. In this series there has been only one case (2%)—in fact, it is the only case that has occurred in this hospital, where at least 80 patients have received reasonably long courses of not less than 150 mg. of chlorpromazine daily. Until the action of the drug in the liver has been fully demonstrated, I feel that one should discontinue treatment while there is any sign of liver damage, and I would be reluctant to use it unless it was urgently indicated, in spite of the finding in the section of liver, which showed no evidence of permanent damage that could be attributed to the chlorpromazine. It is noted that in the other case described, where the patient died, there had been a pause in treatment, and jaundice recurred after treatment was renewed. The possibility of a sensitizing effect must be considered, especially as many psychotic patients, unless under careful observation, may not take all the tablets given and therefore dosage with the drug may only be intermittent.

It is difficult to understand why a demented patient should improve when taking chlorpromazine when she does not do so with other sedative drugs such as paraldehyde. The response is probably due to reduction in tension and response to hallucinations without alteration in the basic dementia. Thus, although the misinterpretations still occur, they are no longer charged with the same degree of tension and the patient can spare time to deal with her immediate surroundings. Sedative drugs merely damp down the cerebral response as a whole, while chlorpromazine acts selectively in a manner similar to the operation of leucotomy, for which reason it has been called the "chemical leucotomy." The possibility of its use as a therapeutic test for leucotomy, even if its effects do not persist, must be investigated.

The question of whether chlorpromazine can restore a chronic mental hospital patient to a condition of health sufficient to enable him or her to be nursed at home or in a home for the aged must also be considered. The patients described here were cases of extreme difficulty, and several of them have improved a great deal, though not enough for discharge. Experience with these, and with less difficult patients in the hospital, suggests that this drug may prove of much value for those patients who are still at home but tend to wander round the house at night and keep the rest of the family awake, or who are somewhat preoccupied with hypochondriacal symptoms. If this is so, it will go some way towards solving the problem of shortage of bed-space and of nursing staff in mental hospitals.

## Summary

In a controlled experiment, where each patient acted as her own control, 46 elderly psychotic women were treated with chlorpromazine ("largactil"), and in 33 (71.7%) cases there was some degree of improvement. Two serious complications, jaundice and fractured femur, were considered, but were not thought to preclude the use of the drug as an aid in the nursing of the difficult patient.

I wish to thank Dr. R. E. Hemphill, medical superintendent, Bristol Mental Hospitals, for permission to use these cases; Dr. D. F. Early for his guidance and encouragement in preparing this paper; Dr. K. R. L. Hall for his help with the statistics; and Dr. W. Sandry for the report on the liver section. I also wish to thank the nursing staff, dispenser, and laboratory staff for their unfailing assistance, and Messrs. May & Baker for supplying the largactil and the corresponding control tablets and injections.

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# L. CANICOLA INFECTION TREATED BY PENICILLIN

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Human infection with *Leptospira canicola* is infrequently recorded in this country although the organism is widely distributed in the canine population. Thus Stuart (1946) has shown that 25 to 40% of dogs in Glasgow are infected with the organism, and Broom and MacIntyre (1948) found similar figures in London. In dogs the organism produces a pyelonephritis, following which the animals may excrete the organisms in the urine for several months (Stuart, 1946).

The literature has been admirably reviewed by Broom (1951). He believes the infectivity to be low, since it is usual to find that only those in a household who have nursed an infected dog and who have cleaned up its dejecta are liable to contract the disease. Although the routes of infection are not known with certainty, the entry would appear to be through intact or broken skin, mucous membranes of the upper respiratory tract, or the conjunctivae. Bathing in contaminated water is a not uncommonly reported mode of infection.

The clinical features are those of an influenza-like illness of sudden onset, with signs of meningeal irritation appearing early in the illness in about two-thirds of cases (Alston, 1949).

We report two further cases arising in Glasgow. One of these was a laboratory infection, and it was possible to estimate the incubation period. Both were successfully treated with penicillin.

## Case 1

Five days before admission to hospital a housewife aged 52 was suddenly taken ill with severe pains in the legs and paraesthesia from the knees to the ankles. On the second day of the illness she began to complain of severe throbbing frontal headache and pain in the neck. On the following day the pains and paraesthesia in her legs disappeared and were replaced by severe backache. On the fourth day of the illness persistent nausea, retching, and vomiting began, associated with an erythematous rash on her legs.

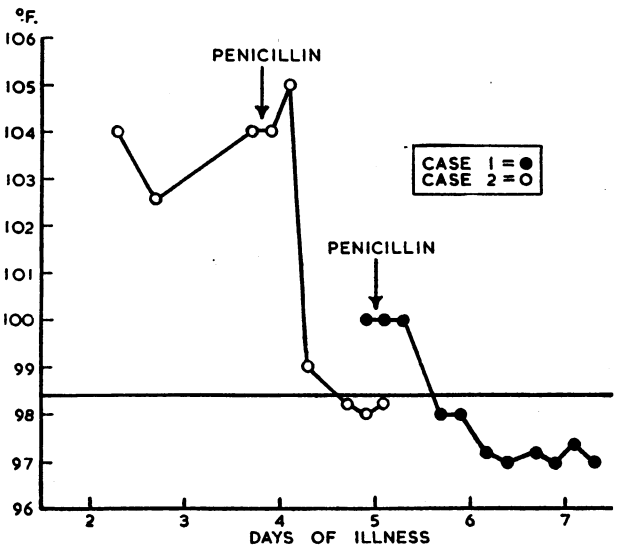
On admission to hospital she was found to be a flushed, rather drowsy woman with a pyrexia of 100° F. (37.8° C.). Discrete erythematous macules were present on the front of both legs, with a pin-point erythema over most of her back. The edge of the liver was palpable, as was the tip of the spleen. Slight neck rigidity was demonstrable. There was no jaundice. The total white blood count was 12,500 per c.mm. (85% polymorphs, 8% lymphocytes, 4% monocytes, 2% eosinophils). The E.S.R. (Westergren) was 40 mm. in the first hour. The urine showed no abnormality.

On lumbar puncture clear fluid was obtained at a pressure of 180 mm. of water. A pleocytosis of 584 cells per c.mm. (86% lymphocytes, 9% monocytes, 5% polymorphs) was present. The chemistry of the fluid showed: protein, 45 mg. per 100 ml.; sugar, 67 mg. per 100 ml.; and chloride, 725 mg. per 100 ml. No organisms were found microscopically or on broth culture.

During the two weeks preceding her illness the patient had been nursing a sick dog, and in view of this the veterinary surgeon who had been treating the dog was consulted. He stated that the dog had been suffering from a renal infection, and, whilst he had no bacteriological evidence of *L. canicola* infection, he thought this a likely diagnosis in view of the frequency of such infection among dogs in Glasgow.

In the light of this opinion, a provisional diagnosis of "canicola fever" was made, and, after blood specimens had been obtained for diagnostic purposes, treatment was instituted with crystalline penicillin, given intramuscularly in doses of 250,000 units six-hourly. This was begun one hour after admission—that is, on the fifth day of illness—and continued until the fourteenth day.

Within 24 hours there was relief of symptoms, and, after 48 hours, apparent clinical cure (see Chart).




Temperature chart of Cases 1 and 2.

*Bacteriology.*—The organism was not obtained on blood culture using ordinary media nor on guinea-pig inoculation, but serological tests confirmed the diagnosis in both the patient (Table I) and her dog, the latter's serum agglutinating *L. canicola* to a titre greater than 1/30,000. The same tests made on members of the patient's household, who had been in contact with the dog, were negative.

The patient was dismissed symptom-free two weeks after admission. A lumbar puncture carried out just before discharge showed a clear fluid under a pressure of 50 mm. of

TABLE I.—*Results of Serum Agglutination Tests in Two Cases of Leptospirosis Canicolaris*

| | Case 1 | | | | | Case 2 | | | |
|---|---|---|---|---|---|---|---|---|---|
| Day of Disease: | 5th | 13th | 23rd | 50th | 72nd | 8th | 19th | 24th | 44th |
| Reciprocals of titres with: | | | | | | | | | |
| *L. canicola* .. .. | 0 | 1,000 | 10,000 | 1,000 | 1,000 | Neg. | Neg. | 1,000 | 1,000 |
| *L. icterohaemorrhagiae* | 0 | 0 | 10 | 0 | 0 | ,, | ,, | 100 | 30 |